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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/469,172	06/06/1995	CHRISTINE SEIDMAN	IGI-111CN	6019

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ELIZABETH A HANLEY
LAHIVE AND COCKFIELD
28 STATE STREET
BOSTON, MA 02109

EXAMINER

MYERS, CARLA J

ART UNIT	PAPER NUMBER
1634	33

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/469,172	SEIDMAN ET AL.
Examiner	Art Unit
Carla Myers	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 25 April 2002.
2a) This action is FINAL. 2b) This action is non-final.
3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-30,32-34 and 36-46 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) Claim(s) _____ is/are allowed.
6) Claim(s) 1-30,32-34 and 36-46 is/are rejected.
7) Claim(s) _____ is/are objected to.
8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.
15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____. 4) Interview Summary (PTO-413) Paper No(s) _____.
5) Notice of Informal Patent Application (PTO-152)
6) Other: _____

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1. The request filed on April 25, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/469,172 is acceptable and a CPA has been established. An action on the CPA follows.
2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-30 and 32-34, 36-46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 5,429,923. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '923 are inclusive of methods for

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diagnosing hypertrophic cardiomyopathy wherein the method comprises detecting the presence or absence of a hypertrophic cardiomyopathy associated mutation in the RNA of an individual.

It is noted that the claims of '923 do not recite packaging the reagent required to perform the diagnostic method in a kit. However, reagent kits for performing DNA diagnostic assays were conventional in the field of molecular biology at the time the invention was made and therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to package the primers and probes required for the detection of hypertrophic cardiomyopathy associated-mutations in a kit for the expected benefits of convenience and cost-effectiveness.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 36 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Eisenberg.

Eisenberg teaches RNA probes complementary to the sequences of *B*-MHC nucleic acids (see page 289). The probes are considered to have the property of being useful for facilitating diagnosis of hypertrophic cardiomyopathy because the probes of Eisenberg hybridize to and thereby are capable of detecting changes in the *B*-cardiac myosin heavy chain DNA. Any probe

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which hybridizes to beta-myosin heavy chain DNA would be useful in detecting a mutation in beta-cardiac myosin heavy chain DNA. The RNA probe of Eisenberg would be expected to hybridize to the beta-cardiac myosin heavy chain DNA since it is complementary to this DNAs sequence and thereby the probe could be used in, e.g. an enzyme digestion method to detect mutations in the DNA sequence. Accordingly, the RNA probe of Eisenberg has each of the properties of the probe of claim 36, i.e., the probe comprises ribonucleotides arranged in a sequence which is complementary to at least a portion of the beta-cardiac myosin heavy chain DNA; the probe has the property of being useful for the diagnosis of hypertrophic cardiomyopathy; and the probe is capable of detecting a hypertrophic cardiomyopathy-associated mutation. Therefore, Eisenberg anticipates the invention of claim 36.

5. Claims 37 and 38 are rejected under 35 U.S.C. § 102(a) as being anticipated by Friedman.

Friedman teaches sets of nested PCR primers useful for the amplification of nucleic acids of *B*-MHC (see page 109). Because the primers of Friedman amplify nucleic acids of *B*-MHC, the primers have the inherent property of being capable of detecting mutations in the *B*-MHC gene, including hypertrophic cardiomyopathy-associated mutations. Accordingly, Friedman anticipates the invention of claims 37 and 38.

6. Claims 37 and 38 are rejected under 35 U.S.C. § 102(b) as being anticipated by Feldman.

Feldman teaches compositions comprising sets of PCR primers useful for the amplification of nucleic acids of *B*-MHC (see page 1867). Because the primers of Feldman amplify nucleic acids of *B*-MHC, the primers have the inherent property of being capable of detecting mutations in the *B*-MHC gene, including hypertrophic cardiomyopathy-associated

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mutations. The compositions of Feldman contain 13 pmol of each primer and therefore are considered to comprise at least 4 oligonucleotides. Accordingly, Feldman anticipates the invention of claims 37 and 38.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 33-34 are rejected under 35 U.S.C. § 103 as being unpatentable over Geisterfer-Lowrance in view of Almoguera and further in view of the Stratagene Catalog.

Geisterfer-Lowrance teaches methods for detecting the presence of mutations associated with hypertrophic cardiomyopathy wherein the methods comprise detecting the presence of point mutations in the *B*-MHC nucleic acids by isolating DNA from individuals affected with hypertrophic cardiomyopathy and sequencing the DNA in order to identify the presence of mutations associated with hypertrophic cardiomyopathy (see, e.g., page 1000). In particular,

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Geisterfer discloses the presence of the missense mutation Arg403Gln and the association of this mutation with individuals having hypertrophic cardiomyopathy. Geisterfer-Lowrance does not teach detecting point mutations associated with hypertrophic cardiomyopathy by first amplifying sample *B*-MHC nucleic acids and performing a RNase protection assay.

Almoguera teaches methods for identifying gene mutations associated with genetically inherited diseases wherein the methods comprise amplifying a DNA sequence by PCR, combining the amplified DNA with a labeled RNA probe in order to form a RNA/DNA hybrid, and performing an RNase protection assay wherein cleavage of the RNA/DNA at regions that are not hybridized as indicative of the presence of a disease associated mutation (see, for example, pages 39-41). In particular, the assay identifies single-base substitutions or point mutations which are considered to be "small alterations" in the DNA. Almoguera states that this provides a very rapid, efficient and sensitive means for detecting the presence of point mutations associated with diseases.

In view of the disclosure of Almoguera, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Geisterfer-Lowrance so as to have detected the mutations associated with hypertrophic myocardiopathy in *B*-MHC nucleic acids by amplifying the nucleic acids by PCR and detecting the presence of mutations by performing an RNase protection assay using a labeled RNA probe in order to have achieved the expected advantages of providing a more rapid, efficient, and sensitive assay for the detection of hypertrophic myocardiopathy associated mutations in *B*-MHC nucleic acids.

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Modification of the method of Geisterfer-Lowrance as discussed above would have resulted in a method for detecting point mutations in the *B*-MHC gene which required the use of the reagents of an RNA probe hybridizable to the *B*-MHC gene, PCR primers for the amplification of the *B*-MHC gene and a RNaseA for digesting unhybridized RNA. It is noted that at the time the invention was made the complete nucleotide sequence of the B-MHC was well known in the art and therefore the generation of primers and probes to perform the amplification/RNase protection assay of Almoguera would have been obvious to one of ordinary skill in the art and well within the skill of the ordinary artisan. The combined references do not teach packaging these reagents required to practice the detection method or instructions for the detection method in a kit.

However, reagent kits for performing nucleic acid diagnostic assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid detection methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primers, RNA probe, and RNase in a kit for the expected benefits of convenience and cost-effectiveness for practitioners of the art. Furthermore, it would have been further prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included instructions in the kit in view of the conventionality of including instructions in kits for facilitating the use of the packaged reagents. It is noted that the

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written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight (see MPEP 706.03(a)).

8. Claims 24-26, 28-30 and 43 are rejected under 35 U.S.C. § 103 as being unpatentable over Geisterfer-Lowrance in view of Mullis.

Geisterfer-Lowrance teaches methods for detecting the presence of mutations associated with hypertrophic cardiomyopathy wherein the methods comprise detecting the presence of point mutations in the *B*-MHC nucleic acids by isolating DNA from individuals affected with hypertrophic cardiomyopathy and sequencing the DNA in order to identify the presence of mutations associated with hypertrophic cardiomyopathy (see, e.g., page 1000). In particular, Geisterfer discloses the presence of the missense mutation Arg403Gln and the association of this mutation with individuals having hypertrophic cardiomyopathy. The reference (see abstract) states that the “(I)dentification of two unique mutations within cardiac MHC genes in all individuals with FHC from two unrelated families demonstrates that defects in the cardiac MHC genes can cause this disease”. Geisterfer-Lowrance does not teach amplifying the sample *B*-MHC nucleic acid prior to determining the sequence of the DNA.

Mullis teaches methods for amplifying nucleic acids by the method of PCR and applies this methodology to assays to detect the presence of point mutations in nucleic acids associated with genetic diseases (see, e.g. col. 2, and 18). Mullis also teaches amplifying nucleic acids by PCR prior to sequencing (see column 36). The reference states that PCR provides the advantages of increasing the quantity of the target nucleic acid and thereby increases the sensitivity of nucleic acid detection and characterization assays. Mullis further teaches that the presence of

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mutations associated with a disease can be detected in a sample RNA by first reverse transcribing the RNA to DNA, amplifying the DNA by PCR and then analyzing the amplified DNA for the presence of disease associated mutations.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Geisterfer-Lowrance so as to have amplified the *B*-MHC nucleic acids prior to sequence analysis in order to have increased the quantity of the target DNA and thereby to have increased the overall sensitivity of the detection of hypertrophic cardiomyopathy associated point mutations in the *B*-MHC nucleic acids.

9. Claim 27 is rejected under 35 U.S.C. § 103 as being unpatentable over Geisterfer-Lowrance in view of Almoguera.

Geisterfer-Lowrance teaches methods for detecting the presence of mutations associated with hypertrophic cardiomyopathy wherein the methods comprise detecting the presence of point mutations in the *B*-MHC nucleic acids by isolating DNA from individuals affected with hypertrophic cardiomyopathy and sequencing the DNA in order to identify the presence of mutations associated with hypertrophic cardiomyopathy (see, e.g., page 1000). In particular, Geisterfer discloses the presence of the missense mutation Arg403Gln and the association of this mutation with individuals having hypertrophic cardiomyopathy. Geisterfer-Lowrance does not teach detecting point mutations associated with hypertrophic cardiomyopathy by first amplifying sample *B*-MHC nucleic acids and performing a RNase protection assay.

Almoguera teaches methods for identifying gene mutations associated with genetically inherited diseases wherein the methods comprise amplifying a DNA sequence by PCR,

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combining the amplified DNA with a labeled RNA probe in order to form a RNA/DNA hybrid, and performing an RNase protection assay wherein cleavage of the RNA/DNA at regions that are not hybridized as indicative of the presence of a disease associated mutation (see, for example, pages 39-41). In particular, the assay identifies single-base substitutions or point mutations which are considered to be "small alterations" in the DNA. Almoguera states that this provides a very rapid, efficient and sensitive means for detecting the presence of point mutations associated with diseases.

In view of the disclosure of Almoguera, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Geisterfer-Lowrance so as to have detected the mutations associated with hypertrophic cardiomyopathy in *B*-MHC nucleic acids by amplifying the nucleic acids by PCR and detecting the presence of mutations by performing an RNase protection assay using a labeled RNA probe in order to have achieved the expected advantages of providing a more rapid, efficient, and sensitive assay for the detection of hypertrophic cardiomyopathy associated mutations in *B*-MHC nucleic acids.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers
May 15, 2002

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER